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A Pilot Study of Vinorelbine on a Weekly Schedule in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck

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VINORELBINE (VNR; 5'-nor-anhydrovinblastine) is a new semi-synthetic vinca alkaloid which has demonstrated activity *in vitro* against several non-small cell lung cancer lines [1, 2] in patients with squamous cell lung cancer, bronchial adenocarcinoma [3], and advanced breast cancer [4–6]. Although it has been suggested that VNR is less neurotoxic than other vinca alkaloids, VNR is however quite myelosuppressive, with granulocytopenia being the major dose-limiting factor. On the basis of the good clinical activity shown by VNR in epidermoid lung cancer, and by vinblastine [7] in squamous cell carcinoma of the head and neck (SCHNC), we tested the antitumour activity and toxicity of VNR given on a weekly schedule in a series of patients with SCHNC.

After informed consent 24 patients (22 males/2 females, mean age 56 years, mean Karnofsky index 75) with biopsy-proven recurrent and/or metastatic SCHNC were enrolled in the study. Patients included 10 laryngeal, 7 oropharyngeal, 3 hypopharyngeal, 3 rhinopharyngeal and 1 maxillary sinus squamous cell carcinomas. Pretreatment included surgery (50%), radiotherapy (33%), and chemotherapy with cisplatin plus 5-fluorouracil (25%). 2 patients were previously untreated. Sites of disease included loco-regional disease (75%), node (17%), lung metastasis (12.5%), liver (8%), soft tissue (8%). VNR [20 mg/m²/week intravenously (i.v.) diluted in 250 μl normal saline] was given over 20 min to the first group of 3 patients, and then escalated by 5 mg/m²/week for subsequent groups of patients until the maximally tolerated dose was reached (Table 1). Patients received ondansetron (8 mg i.v.) as antiemetic therapy. Although 20 and 25mg/m²/week VNR was quite well tolerated, we were not able to increase VNR above 30 mg/m²/week because of the occurrence of grade 4 leukopenia in 1 case, grade 3 leukopenia in 2 patients, and grade 2 neuromotor toxicity in 1 patient. Thus, all further patients received VNR at a dosage of 25 mg/m²/week.

Over a total of 286 weeks of VNR therapy (11.9 weeks/patient), 22 patients (92%) had haematological toxicity: 7 patients (29%) had grade 3 granulocytopenia, 2 (8%) showed grade 4 granulocytopenia, and 8 (33%) grade 1–2 thrombocytopenia. Grade 2 vomiting was seen only in 29% of cases, grade 1 oral mucositis was recorded in 2 patients (8%), and a slight increase (< two times normal value) in serum bilirubin in 2 cases (8%). 5 patients (21%) had grade 1–2 neurotoxicity: 4 patients (17%) had grade 1–2 constipation, 3 patients (12.5%) had grade 1 paraesthesias, and 2 patients grade 1–2 impaired speech. 4 patients (17%) complained of pain in the injection site.

Table 1. Dose escalation of weekly VNR and related side-effects

Dose level	Patient no.	Toxicity (WHO grading)	
20 mg/m²/week	1	Leukopenia	1
	2	Leukopenia	1
		Local pain	1
	3	Leukopenia	2
		Constipation	1
		Neurosensory (paraesthesias)	1
25 mg/m²/week	4	Leukopenia	2
		PLT	1
		Constipation	2
	5	Leukopenia	3
		Nausea	2
	6	Leukopenia	2
		Anaemia	1
30 mg/m²/week	7	Leukopenia	4
		PLT	2
		Nausea	1
	8	Leukopenia	3
		Vomiting	2
		Neurosensory (paraesthesias)	1
	9	Neuromotor	2
		(impaired speech) Leukopenia	3

PLT = Thrombocytopenia.

Of the 23 patients evaluable for response (WHO criteria) [8], 5 (22%; 95% confidence limits 18–26%) showed a partial response (PR) with a mean duration of 5.8 months (range 3.4–8.3), 7 patients (30%) had no change (NC) in status with a mean duration of 4.3 months (range 3.0–5.8), and 11 had progressive disease (PD). No major objective response was recorded among patients pretreated with chemotherapy. The mean survival of patients with PR was 7.4 months (3.6–9.5), and that of patients with NC and PD was 5.7 months (3.2–6.8) and 4.6 months (2.5–5.8), respectively. Among partial responders there were 2 previously untreated patients with locoregional disease at oropharynx, 2 pretreated with radiotherapy presenting soft tissue metastasis of rhinopharyngeal carcinoma and locoregional recurrence of laryngeal tumour, respectively, and 1 patient with nodal recurrence of operated laryngeal cancer. In conclusion, data from this pilot study, although preliminary, suggest that VNR is active against SCHNC. It may be safely administered at the dose of 25 mg/m²/week on an outpatient basis. Thus, it may be worthwhile to investigate VNR in further phase II trials in association with other drugs, such as cisplatin plus 5-fluorouracil [9, 10] in order to increase the objective response rate of the latter combination.

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Correction

Expression of Homeobox-containing Genes in Primary and Metastatic Colorectal Cancer—This paper was published in *The European Journal of Cancer*, Vol 29A, No. 6, pp. 887–893. Unfortunately, the abbreviation HOX was misued in several places in The Introduction; this has now been amended and a corrected version of The Introduction follows.

INTRODUCTION

COLORECTAL CARCINOMAS rank high among the most frequent human malignancies. Such tumours may arise from benign adenomatous polyps, which later progress to adenocarcinomas through several mutational steps [1]. Some of these events have been better understood through the identification of the genes 'Familial Adenomatous Polyposis' (FAP) and 'Deleted in Colorectal Cancer' (DCC) involved in colon tumorigenesis [2–3]. The overall biological characteristics of colorectal cancers, and of neoplastic tissues in general, result from accumulated genetic alterations rather than from the order in which these events occur with respect to one another [1]. Even though several important genes have been identified, other events, which remain to be elucidated, may well take place during the progression of colon cancer.

Homeobox genes are a family of genes containing a common 183-nucleotide sequence. The homeobox encodes a 61 amino acid domain, the homeodomain (HD), which includes a helix-turn-helix motif responsible for the DNA binding ability of homeobox-containing proteins [4]. On the basis of structural similarities and direct evidence that *Drosophila* homeodomain proteins are capable of binding DNA sequences and modulating transcriptional activity, it is generally accepted that homeodomain proteins are transcriptional regulators [5]. The homeobox was originally discovered in genes controlling *Drosophila* development [6] and has subsequently been isolated in other, evolutionarily distant species, such as nematodes and vertebrates [7]. Different homeobox gene families have evolved which encode homeodomain of different types or classes. Among these HD the *Drosophila antennapaedia* (Antp) homeodomain defines one consensus sequence referred to as class I HD [4]. Mammalian class I homeobox (HOX) genes are clustered in restricted regions of the genome (HOX loci) on four distinct chromosomes that presumably evolved by duplication of a primordial gene cluster [8]. A striking finding is that the order of genes within each cluster is also highly conserved throughout evolution, suggesting that the physical organisation of HOX genes may be essential for their expression [10]. HOX genes are expressed during embryogenesis in a tissue-specific and frequently stage-related fashion [11]. Expression of individual HOX genes has been detected in normal adult tissues [8–12].

A possible association between genes that control transcription and those involved in the oncogenic process has been postulated on the basis of several independent observations. Constitutive expression of the HOX-2.4 gene may entail oncogenic consequences in mice [13]. Mice homozygous for a null mutation in the HOX-1.5 and HOX-1.6 genes show major morphological abnormalities [14–15]. The growth factor activin activates homeobox gene expression in developing Xenopus embryos [16]. The coordinate regulation of HOX genes may play an important role in human haemopoietic differentiation [17]. HOX gene expression appears to be altered in renal cancer compared to normal human kidney tissues [12].

In line with the above association between HOX genes, development and oncogenesis, our aim has been to determine whether the physical organisation of HOX genes might be a part of a regulatory network involved in the control of such processes. We have thus analysed the expression of a panel of 38 HOX genes in adult human tissues originating from normal intestinal mucosa or liver parenchyma from colorectal carcinoma biopsy samples and liver metastases from colorectal cancers. We have identified HOX genes (HOX1J, HOX2F) whose expression remains unaltered during progression of colorectal tumours. We interpret this result as an intestinal-specific expression which may suggest the involvement of the corresponding homeoproteins in organ-specific functions. Expression of other HOX genes (HOX2C, HOX4F), however, is altered in primary and metastatic colorectal cancer suggesting the possible implication of these transcriptional regulators in colon tumorigenesis.